Environmental Health Perspectives
Vol. 34, pp. 223-225, 1980

International Commission for Protection Against Environmental Mutagens and Carcinogens

ICPEMC News No. 2

ICPEMC is an international commission with scientific expertise in the fields of environmental mutagenesis, carcinogenesis and genetic toxicology. Its membership is recruited from universities, research institutions, industry and national health authorities. Its principal objective is to prevent and minimize the deleterious effects resulting from the interaction of chemicals with the genetic material of man. The Commission seeks to identify and promote scientific principles and to make recommendations that may serve as the basis for guidelines and regulations in the national or international context. ICPEMC has two main strategies to achieve its objectives: The preparation of critical evaluations of the current body of knowledge that may serve as a basis for establishing priorities for further research or possible regulatory action, and identification of substances and situations that may entail significant genotoxic damage to man.

The Commission meets at regular intervals, for the time being in April and September at Verte Rive near Lausanne. The Executive Committee, consisting of the ICPEMC officers (*1*) the president of IAEMS, and the Vice-Chairman for liaison with the Institut de la Vie, exercises general oversight of ICPEMC and its committee-activities and acts for the Commission between meetings.

In the first meetings, considerable attention was given to defining the aims and objectives of the Commission, in particular to the way the Commission should work. Agreement was reached that the Commission should primarily function in a scientific manner, as set out above, and refrain from making statements carrying regulatory implications.

The organizational structure of ICPEMC has been formalized in a constitution that, after intensive debate in various meetings, was adopted by unanimous vote of the Commission in its fourth meeting in September 1978. The establishment of ICPEMC as a nongovernmental organization will facilitate liaison with organizations that share its interest in resolving problems posed by mutagens and carcinogens in the human environment, such as UNEP, WHO, EEC, and various other institutions. In this context it may be noted that ICPEMC is affiliated with the International Association of Environmental Mutagen Societies and sponsored by the Institut de la Vie.

Task groups and committees have been established by the Commission. Task groups are composed mainly of Commission members, while the membership of committees consists mainly of scientists who are not members of the Commission. The idea behind these ground rules is to achieve some distribution of labor. Moreover, to widen the available expertise, consultants can be appointed to either body.

Task Group 1, consisting of B. A. Bridges (chairman), N. P. Bochkov, H. Böhme, J. Clemmesen, D. Jansen, T. Sugimura, and L. Tomatis, sets the priorities for evaluating the genotoxic properties of chemicals. These compounds are selected by Task Group 1, after correspondence and consultation with Commission members. Human exposure constitutes an important criterion for selection and review by ICPEMC. The procedure adopted so far has been that a first draft is prepared by one or more Commission members. This working paper is circulated to all members, amply discussed in a meeting of the Commission, and subsequently revised. Small editorial groups are constituted during the meeting. They are composed of different members than those responsible for the first draft, so as to achieve distribution of work load and maximum objectivity. The first document resulting from these activities is entitled "Cigarette smoking — does it carry a genetic risk?"; this paper has now been published (*2*) as ICPEMC Publication No. 3. Other documents are being prepared on isoniazide, epichlorohydrin, dichlorvos, vinyl chloride, hair dyes, and psoriatics.

Task Group 2, consisting of B. Matter (chairman), J. Drake, A. Hollaender, B. J. Kilbey, C. Ramel, V. Ray, and K. Sundaram, has prepared an advisory on the strategy for employing the best short-term screening systems available at present. This report,

entitled "Advice on screening of chemicals for Mutagenicity" has been published (*3*) as ICPEMC Publication No. 2. ICPEMC encourages the use of the available tests and urges that a flexible attitude be adopted when selecting test systems. To increase the chances of detection, supplementation with metabolizing extracts from mammalian tissues is recommended. A combination of different assay systems obviously augments the possibility that different kinds of genetic damage are recovered. Reference is made to the report of the European Environmental Mutagen Society entitled "Mutagenicity Screening, General Principles and Minimal Criteria" (*4*).

Task Group 3, consisting of B. A. Bridges (chairman), N. P. Bochkov, and J. D Jansen, prepared a statement recommending genetic monitoring of human populations accidentally exposed to a suspected mutagenic chemical" which has appeared in the literature (*5-7*). In brief, its contents are the following. When groups of people are accidentally exposed to high concentrations of toxic chemicals, as they were at Seveso in 1976, the health authorities' first concern is quite rightly with acute toxicity and possible teratogenic effects. However, when the chemical is a mutagen, there will be questions concerning damage to the victim's genetic material and the possibility that genetic or carcinogenic effects appear many years after the exposure. At present, these questions cannot be satisfactorily answered, because too little is known about chemical mutagenesis in man. Obviously accidents are most regrettable, but it is reasoned that valuable scientific information can be obtained by careful and systematic study of the exposed groups and their progeny. Thus the following measures are recommended: (1) rapid identification of the exposed population, and quantitative estimates of the exposures suffered; (2) assessment of possible mutagenic effects in the somatic cells of the exposed individuals, employing various detection techniques; (3) long-term monitoring of the accidentally exposed populations for the incidence of malignancies, and their offspring for genetic effects, such as spontaneous abortions and congenital malformations. Knowledge thus obtained will not only be of benefit for appropriately counseling the exposed individual, but will also provide the scientific basis required for evaluating future exposures of populations to mutagenic chemicals. The magnitude and associated costs of the effort involved and the unpredictability of when accidents may occur, make early preparation for such studies and their implementation an absolute necessity.

Task Group 4, consisting of A. Hollaender (chairman), V. Ray, T. Sugimura, and L. Tomatis, is engaged in formulating a statement on possible tolerance limits or limits of exposure to mutagenic chemicals at which no detrimental effect can be recognized.

Committee 1, chaired by B. J. Kilbey, is charged with reviewing the development, validation, application, and comparison of short-term screening systems for identifying and characterizing chemical mutagens. The first meeting took place at Versailles from September 22 to September 25, 1978, and two main areas were discussed: the criteria which the tests should fulfill to be recommended by ICPEMC and the work of the Committee during 1979. The criteria for suitable screening tests for mutagens can be summarized as follows: (1) the damage scored in the test should be damage believed to be of significance to man himself; (2) the test system should have the capacity for metabolizing the compound under consideration, if possible in a way which reflects metabolism in man. In addition the test should fulfill the following operational standards: it should give consistent results when used in different laboratories and in repeats in the same laboratory; the results it gives should be concordant with the other systems used to screen for mutagenesis; the test should be validated with respect to the response of whole mammals as is done for carcinogenicity; the test should be as sensitive as possible to the mutagenic effects of nontoxic doses; the test should be cheap and rapid. A plan was developed to collect the above information for a number of different test systems, that have been used with a great number of different mutagenic chemicals. All compounds tested in the whole mouse test will also be included since these will form a useful starting point for validating the screening tests.

Committee 2, chaired by D. B. Clayson, studies the relationships between chemical carcinogens and chemical mutagens. The Committee met at Versailles, December 4-6, 1978. The first two days of the meeting were occupied with the presentation of working papers and verbal reports prepared by the various Committee members. Working papers prepared by D. B. Clayson, entitled "Differences between *in vivo* and *in vitro* systems," by A. S. Wright, entitled "Metabolic differences *in vivo* and *in vitro*," and by P. Brookes on "Cell transformation" are now being circulated to Commission members, so that, hopefully, in due time they can appear as ICPEMC papers.

The aims of Committee 2 were redefined to separate them more clearly from those of Committee 1. These tasks are now to investigate: (1) to what extent are mutagenicity tests predictive of carcinogenicity? (2) to what extent are transformation assays predictive of carcinogenicity? (3) is there a causal relationship between mutagenicity and carcinogenicity? (4) is there a quantitative relationship between mutage-

nicity and carcinogenicity? (5) is there a relationship between *in vitro* transformation and mutagenicity? Written reports bearing on these questions will be prepared over the years 1979 and 1980, by the various members of Committee 2.

Committee 3, chaired by E. Poulsen, is preparing an ongoing registry of national regulatory principles and actions. The first meeting of Committee 3 took place at Versailles, October 24-26, 1978. The task of the Committee was discussed and interpreted. Data sheets for the individual countries were developed. They will be divided into those for Group I countries, consisting of EEC countries, Northern countries, Austria, Switzerland, North America, COMECON member states, and Japan, and those for Group II countries, that is, other countries for which information can be obtained. International guidelines and proposals will be considered at the next meeting of the Committee. P. Elias, will, in collaboration with S. Igali, Y. Tazima, and C. J. Damme, develop the four regional reports covering the Group I and II countries by summer 1979, based on the guidelines that were agreed upon in Versailles.

Committee 4, chaired by M. F. Lyon, is charged with evaluation of risk estimate procedures of mutagenic chemicals and the development of practical exposure limits. The first meeting of the Committee took place on July 12-13, 1978 in Dublin. The Committee rearranged its task to comprise: (1) dose-response relationships, covering: definition of dose, dose-response curves, and pharmacokinetics; (2) interaction of agents, mammalian systems; (3) sensitivity of germ-cell stages; (4) spectra of induced genetic changes; (5) extrapolations from one species to another and one cell type to another and structure-activity relationships from one chemical to another; (6) genetically significant doses; (7) methods of estimating resultant genetic damage. Reports on these various topics will be prepared and considered at the next meeting.

Committee 5, to be chaired by J. R. Miller to consider an epidemiological approach to the possible mutagenic consequences of exposure to environmental agents, will start its activities in 1979.

In order to achieve maximum coordination and interaction between the five ICPEMC Committees, the Commission decided to organize a simultaneous meeting of all five committees in 1979. This meeting is scheduled for September 17-20 at Château de Ripaille in Thonon.

A request was received from the U.S. National Academy of Sciences to provide the data available on the mutagenic effects of saccharin. Following a request by the secretary to all members both of the Commission and the four committees of ICPEMC, some 20 documents were received and transmitted to the secretary of the National Academy. It is worth noting that this is the first time that ICPEMC was requested to provide information on the mutagenic effects of a special chemical by an "outside" institution. In this context it is also of interest to mention that the National Swedish Environmental Protection Board has asked ICPEMC to act in an advisory capacity concerning an evaluation of the available systems for mutagenicity testing which can serve as a basis for decisions taken within government organizations and industry and to provide a system in the field of evaluation of genetic hazards due to chemical substances.

Informal liaison has been established with UNEP and WHO, in that observers from both organizations have attended the second, third, and fourth Commission meetings in Lausanne. A request from WHO was received to send an observer to a meeting on the health effects of smoking. This was arranged through the International Association of Environmental Mutagen Societies.

ICPEMC received an invitation from UNEP to send a representative to the 7th session of the Governing Council of the United Nations Environment Program in Nairobi from April 18-May 4, 1979. Contacts have also been established with the International Commission on Radiation Protection (ICRP) and the International Agency for Research on Cancer (IARC). The Secretary received a large number of requests for information and provided relevant material concerning ICPEMC and its activities. Financial support was received in 1978 also from the Commission of the European Communities, Directorate-General for Research, Science and Education.

The help of Professor Maurice Marois and his staff in organizing the meetings of the Commission and committees in Lausanne and Versailles is gratefully acknowledged.

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